Amendments to the Specification:

Please replace paragraph [0001] with the following amended paragraph:

[0001] This application is a continuation of PCT/US02/35163 filed 11/04/2002. This invention relates to fluid lock systems for indwelling catheters and to flushing procedures, solutions, and methods for maintaining the patency of fluid locked systems.

Please replace paragraph [0002] with the following amended paragraph:

[0002] Intravenous catheters represent the most common parenteral site for medication delivery. A large portion of these catheters, placed in either a peripheral or central vein, are left in situ for extended periods of time. Commonly these catheters are connected with tubing systems having closed sealed ends. These tubing systems are filled with a flush solution, which is injected through a seal or valve at a proximal terminal of the system. The act of injecting and filling with solution, a blind ~~blinded~~ ended tube in fluid connection with a blood vessel has been termed a "lock procedure" because it sets up, in fluid connection with flowing blood, a simple and relatively static, vacuum-locked column of solution, extending from the solution-blood interface to a sealed proximal terminal. Within a resting fluid locked system, the pressure is relatively uniform and is substantially equal to the pressure of the flowing blood. The fluid lock system

generally has a relatively fixed volume and limited elasticity so that variations in pressure within the flowing blood cannot cause substantial net or reciprocating flow of fluid between the

locked system and the blood vessel. Although the term "heparin lock" or "saline lock" has been widely used, alternative flush solutions may be used. For this reason the term "fluid lock" or "lock" is preferred to designate such a procedure and/or system (which includes or is otherwise connectable to a catheter).

Please replace paragraph [0004] with the following amended paragraph:

[0004] Other than leakage, the most important modes of failures of a conventional lock system are either thrombotic, infectious, or a combination of both. The rate of thrombotic failure has been reported to exceed 10%. One of the factors precipitating failure is reflux of blood into the tip of the catheter lumen associated with an inadvertent internal volume reduction of the fluid lock. Today the proximal seals of fluid locked systems are most commonly luer receiving valves or cannula receiving septae. As is standard with the lock procedure, these terminals generally automatically seal upon withdrawal of the cannula or luer after a flush maneuver, however, with many such systems, such withdrawal can result in removal of a small volume of fluid from the locked fluid column causing reflux of blood into the catheter lumen to accommodate that volume loss. U.S. patent application Publication No. 20010039403 published Nov. 8, 2001, of the present inventor, (the entire contents of which is incorporated by reference as if completely disclosed herein) <u>discloses</u> ~~disclose~~ a positive flow generator for flushing indwelling fluid lock medical systems and for displacing such refluxed blood back out of the catheter tip.

Please replace paragraph [0005] with the following amended paragraph:

[0005] Another factor precipitating failure of a fluid lock is the common state of facilitated diffusion, which develops at the leading edge of the locked fluid. Over time, diffusion, facilitated by the minor pressure variations in venous blood at the catheter lumen-to-blood interface causes blood components to gradually invade the distal end of the lumen of a fluid locked catheter. This process also induces migration of flush solution constituents from the lock ~~locked~~, such as the anticoagulant or antimicrobial and this can contribute to failure. Peripheral catheters, being protected from central pressure variations by distance and venous valves, are exposed to much less pressure variation than central catheters and these catheters are commonly filled with saline alone. However, some blood still slowly penetrates the lumen at the tip of these catheters. For this reason ~~reasons~~ it is common hospital protocol to flush such peripheral catheters every eight hours or so, to displace the small volume of blood, which enters the tip (if no scheduled infusion of medication has been provided during that interval which would otherwise achieve that goal).

Please replace paragraph [0006] with the following amended paragraph:

[0006] To flush the lock system and its fluid connected catheter lumen, sterile saline or other flush solution is commonly aspirated from a multi-dose vial. Since, at the present time, most drug vials have elastomeric septae intended for receiving a sharp needle, this aspiration procedure often requires a disposable adapter to prevent needle sticks, which

adds to the general ~~the~~ cost of the lock procedure. A simple saline flush also requires a sterile syringe and, with some systems, a sterile cannula connected with the syringe, each further adding to the expense. Because multi-dose vials carry the risk of cross contamination if not managed properly and because time dependent personnel costs are progressively rising in hospitals, an alternative, pre-filled disposable saline flush syringes ~~syringe~~ are being offered by corporations. However the storage of sterile flush solution within individually packaged syringes is also expensive, and such devices can cost in excess of $.50 for a single unit. There are hundreds of millions of such procedures performed in the US each year so that, considering all related costs, the expense of maintaining locks in the US alone probably exceeds several 100s of millions of dollars.

Please replace paragraph [0007] with the following amended paragraph:

[0007] In addition to the expense, each time the lock system is reentered the infection risk is increased to the patient because the outside instrument (such as a cannula, luer, or needle) can carry bacteria and yeast into the lock where they can proliferate and induce bacteremia and/or fungemia which are associated with considerable expense and can be fatal). In the 21st century many more patients have been subjected to transplantation or otherwise have reduced immune systems making it more important to reduce routine entry of external devices into lock systems as much as possible. The catheter hub and internal lumen, have long posed ~~as~~ an important infection risk problem for patients at home or in hospitals and the contamination risk is directly related to the number of entries into the system. Because each occurrence is associated with some risk, procedures associated with repetitive reentry (as with

periodic flushing) are important access mechanism for microbial invaders. Considered collectively, throughout the United States, each year there are a vast number of such entries into lock systems ~~system~~ for the purpose
of flushing alone, for this reason, although the infectious risk of each flush maneuver is low, the number of patients who die each year due to a contamination during a routine flush, although difficult to measure, is probably quite high. In addition, although each event is again associated with a low occupational risk, the nurse remains potentially exposed to infectious material, and potentially infectious waste is generated, anytime a disposable device such as a cannula enters a tubing system connected to a patient's ~~patients~~ vascular system.

Please replace paragraph [0008] with the following amended paragraph:

[0008] Central catheters are exposed to substantially greater pressure variations, and are often left in for many weeks, and pose an increased risk in the event of lock entry related colonization. Furthermore, the state of facilitated diffusion is heightened with these catheters and thrombus formation can readily occur, causing catheter occlusion and, at times, dangerous thrombus propagation. This is especially true in patients with malignancy, which often produces a state of hyper coagulation. Clot formation can also
contribute to catheter related infection and bacteremia. The extent ~~extend~~ of facilitated diffusion, combined and potential, for relative states of thrombophilia in patients with combined morbidities, produces an environment wherein optimal prevention of occlusion and infection of central catheters requires meticulous and expensive catheter maintenance.

Please replace paragraph [0012] with the following amended paragraph:

[0012] The present inventor recognized that one important fundamental problem with conventional locked systems is that; the actions taken toward achieving the goal of prevention of infection and those toward the goal of prevention of thrombosis are potentially competitive. Frequent entry into the proximal terminal to provide flushing to prevent thrombosis can induce infection whereas; minimization of entry to reduce the risk of infection can induce thrombosis. The present inventor recognized that, it would be preferable, toward the goal of minimizing both risks, to develop a lock system, which could be entered once and flushed many times. Further is was recognized by the present inventor that the efficacy of specialized lock formulations such as, BDTA-antimicrobial combinations, would be enhanced, without the need for additional entry into the locked system and with minimal administration of these formulations to the patient, if these formulations could be stored in a lock system and intermittently advanced forward in small increments to replace lost constituents at the solution-to-blood interface.

Please replace paragraph [0013] with the following amended paragraph:

[0013] According to one aspect of the invention a system is provided including a specialized flush solution formulation containing a beneficial agent, such as an antimicrobial and/or anticoagulant, and a reservoir fluid-locked with a catheter for storing the formulation, the reservoir defines an internal space filled with the formulation in fluid communication with a blood vessel through a lumen within the catheter. The space has an internal pressure essentially equal to the pressure within the blood vessel, such that the

formulation within the lumen interfaces with blood within the blood vessel at a relatively static formulation-to-blood interface adjacent the distal end of the lumen. The system includes a volume reducer for engaging the reservoir and for reducing the volume of the formulation contained within the ~~said~~ space by facilitating the movement of at least a portion of the formulation into the interface to increase the concentration of the formulation along the ~~said~~ interface, the volume reducer preferably includes an element for reducing the volume of the reservoir by predetermined discrete and limited increments at a plurality of different times to increase the efficacy of the formulation with a minimum of transfer of the formulation into the patients blood vessel.

Please replace paragraph [0014] with the following amended paragraph:

[0014] According to one presently preferred embodiment the present invention, a closed system, such as a fluid locked tubing system, is provided with at least one sealed proximal terminal, which can be a luer receiving valve or cannula receiving septum. The closed system is connectable with, or integral with, at least a portion of an indwelling catheter residing beneath a patient's skin and/or vein. The closed system defines an internal volume and is at least partially filled with flush after a flush maneuver ~~through~~ is injected through at least one proximal terminal by an external flush system such as a syringe. A residual flush volume of flush solution, such a mixture of antimicrobial and anticoagulant (as described in U.S. Pat. No. 6,187,678), remains within the tubing system after a flush maneuver and the aforementioned internal volume defines this residual flush volume. This volume of fluid, in its locked state after the flush maneuver has been

completed and enough time has passed for equalization, has generally an equal pressure to the pressure of the blood at the blood-to-flush solution interface of the locked system.

According to one aspect of the present invention, the pressure of the residual flush solution is intermittently increased and the fluid advanced by intermittent and progressive reduction of the internal volume of the system. The reduction of the internal volume is preferably achieved by a volume reducer, which displaces the volume from a more

proximal position toward a more distal position so that residual fluid is displaced toward the blood-to-flush solution interface of the catheter lumen. The volume reducer can be a single reducer, which provides multiple levels of reduction, and which is intermittently activated to achieve progressively a greater level of reduction of internal volume. Alternatively, the reducer can be comprised of a plurality of multiple elements such as a plurality of small clamps, such as pinch clamps with elongated or flattened compressing surfaces, for compressing and thereby reducing the volume of the tube. These elements can be separate and slidable so that they can be conveniently positioned on the tube,

depending on tape down considerations, or they can be integral or otherwise connected or connectable to the tube. Alternatively selectable volume reducing elements can be

provided as connected or connectable to either or both of the proximal or distal terminals or can be integral with, and/or comprise a portion of the proximal and or distal terminal. As another alternative according to the present invention multiple elements such as clamps may be molded together as a single piece connected by a flexible elongated living

hinge for mounting with an extension tubing set so that the tubing remains flexible when the connected elements are mounted with it. The elements are preferably either injection molded separately or together using a suitable medical grade polymer such as

polypropylene or nylon. [[,]] Alternatively for greater clarity and to enhance its appearance, the elements may be molded of polycarbonate or a polycarbonate- polyester blend may be used. The living hinge can be of the type described in U.S. Pat. No. 5,514,117, which is assigned to the present inventor (the entire contents of which is incorporated by reference as if completely disclosed herein) and marketed by Abbott laboratories under the trade name Lifeshield Connector. The tube is preferably flexible and is preferably comprised of a medical grade polymer, which has known compatibility with medication. For example a short segment of conventional intravenous tubing in wide use as extension sets is suitable for this purpose; however tubing molded with enlarged
regions for compression can also be used to reduce the length of the clamps or increase the volume of the displaced flush solution.

Please replace paragraph [0015] with the following amended paragraph:

[0015] One preferred catheter-flushing system for intermittently flushing the lumen of an indwelling catheter, wherein the catheter has an indwelling portion beneath the skin of a patient, includes a patient mounted tubing system in fluid connection with the indwelling
portion. The tubing system defines an internal volume and at least one proximal terminal for intermittent connection with an external fluid source. The proximal terminal includes a seal for promptly sealing upon disconnection of the fluid source from the terminal. At least a portion of the flush solution entering the tubing system through the terminal remains sealed within the ~~said~~ tubing system after the fluid source has been disconnected from the system, thereby defining a

residual volume of flush solution within the tubing system. The system also includes a volume reducer, which is configured to induce a reduction in the volume of flush solution within the lock system. In the presently preferred embodiment the reducer is configured for progressively reducing the internal

volume of the tubing system at a plurality of different times to displace a plurality of fractions of the residual volume into the indwelling portion of the catheter to intermittently flush the indwelling portion with the flush solution. The activation of the volume reducer preferably and/or its elements reduces the volume within the tubing system by at least one discrete volume. Preferably a plurality of activations of the volume reducer, and/or its elements, reduces the volume within the ~~said~~ tubing system by a plurality of discrete volumes at a plurality of different times to provide intermittent

flushing of the ~~said~~ catheter portion over a prolonged time interval. The flush solution is preferably saline or a mixture of diluent and at least one of an anticoagulant and an antimicrobial agent. These flush solutions are "stored" in the lock system. In the presently preferred embodiment these flush solutions are stored within the tubing system of the locked system, and are intermittently propelled forward as in discrete boluses to enhance the antimicrobial and anticoagulant efficacy of the solutions within the catheter-flushing system and to mitigate the influence of time dependent dilution adjacent the flush fluid-blood interface. If preferred the sequence can be automated such that the reducer reduces the volume at pre-selected intervals.

Please replace paragraph [0016] with the following amended paragraph:

[0016] While the application of a volume reducer, which progressively reduces the

internal volume of the lock, is presently preferred, in another embodiment the reducer achieves a net reduction of flush solution without a permanent change in internal volume of the lock system. This embodiment includes a diffusion facilitator, such as a separate alternating pressure generating element such as a vibratory element or sound emitter for alternating the pressure within the lock to facilitate ~~of~~ the movement of flush solution
within the lock system and preferably within a fluid reservoir comprising a proximal portion lock system. With this embodiment the adverse effects of facilitated diffusion induced by pressure variations within the distal blood vessel are offset by the intermittent provision of pressure variations within the proximal lock to move flush solution and any associated anticoagulant forward in the lock and thereby achieve dilution of the invading blood components at the tip of the catheter lumen which effectively dilutes the components of the clotting cascade preventing thrombosis. With such a system, while blood components slowly enter the system, rather than summarily flush them out in discrete volume reduction maneuvers, their potential to induce thrombus is mitigated by the intermittent facilitated movement of a higher concentration of flush solution with or
without anticoagulant and antimicrobial components toward the distal end of the catheter lumen.

Please replace paragraph [0017] with:

[0017] In one embodiment the system includes a tube for mounting with a patient, the tube has a distal end connectable to the catheter and at least one proximal end with a

terminal for intermittent connection with a source of flush solution. The terminal includes a seal for sealing the ~~said~~ proximal end of the tube when the source of flush solution is disconnected from the terminal. The tube further defines an internal open space defining a internal volume which is reducible, and a lumen extending ~~there~~ through from the sealed proximal terminal to the distal end, so that when a source of flush solution is connected to the terminal, flush solution can enter the tube from the fluid source through the terminal and flow through the lumen to at least partially fill the internal space. The lumen defines at least a portion of the internal volume. The system further includes a volume reducer comprised of at least one volume-reducing element. The volume reducer

is sized and configured to sequentially reduce the internal volume of the tube at a plurality of different times after the distal end has been connected with the catheter, the flush solution has been flowed into the space from the source, and the source has been disconnected from the terminal. In one embodiment the tube is elongated and has different diameters along its length.

Please replace paragraph [0019] with the following amended paragraph:

[0019] Disposing a patient mounted tubing system in fluid connection with the indwelling portion of the catheter, wherein the system has at least one proximal terminal. The tubing system defines an internal space, defining an internal volume.

Please replace paragraph [0020] with the following amended paragraph:

[0020] Flowing flush solution from an external fluid source, through ~~the~~ at least one terminal and through the ~~said~~ tubing system into the indwelling portion, with at least a portion of the solution at least partially filling the internal space.

Please replace paragraph [0024] with the following amended paragraph:

[0024] In the case of a central catheter this residual flush solution can represent the expensive mixture of saline and an anticoagulant with or without an antimicrobial. In the peripheral catheter this is commonly saline alone. However, in either case the present inventor recognized that the presence of the residual fluid could be exploited to enhance the maintenance of patency of indwelling catheters and to prevent the need for frequent outside flushes of the system. The present inventor recognized that a system could be constructed which provided ~~provide~~ intermittent flushes from the residual fluid contained within a closed tubing system connected with a catheter thereby reducing cost, nurse exposure and work time, and catheter contamination risk. Upon the realization, the present inventor developed a sequential catheter flush generation system, which retains the advantages of simplicity and convenience of a basic lock system, but which provides for activation of a sequence of small discrete displacement volumes to be delivered at selected intervals from the locked system to maintain catheter patency without the need to open or enter the system.

Please replace paragraph [0025] with the following amended paragraph:

[0025] Another ~~According to another~~ aspect of the present invention comprises a system for maintaining ~~at least one of~~ the patency and sterility of the lumen of a catheter ~~the~~ system within a blood vessel, the blood vessel containing flowing blood. The lumen defines a distal end within the blood vessel. The system contains a flush solution mixture of a diluent, such as saline, and at least one of an antimicrobial and anticoagulant stored in a fluid locked reservoir, such as a tubing system, in fluid communication with a blood vessel through a lumen, the reservoir has an ~~a~~ internal pressure essentially equal to the pressure within the blood vessel and the flush solution within the reservoir interfaces with blood within the blood vessel at a solution-to-blood interface adjacent the distal end of the lumen. The system includes a volume reducer for periodically reducing the volume of the reservoir to advance the mixture toward the interface to flush blood components from the lumen and to increase the concentration of the mixture adjacent the interface, to thereby increase the efficacy of the mixture with a minimum of delivery of the mixture into the patient's ~~patients~~ vascular system.

Please paragraph [0035] with the following amended paragraph:

[0035] As shown in Figures 2-4 ~~FIG. 24~~, the catheter-flushing clamp 102 has a locking arm 114, with an top surface 115 for application of thumb pressure and an elongated, upper compression surface 116 and a pair of proximal curved hinges 118 connecting the locking arm 114 to a base 120 which projects under and opposes the locking arm 114. The base 120 includes an elongated, lower compression surface 122. The base 120 also includes a distal flexible post 124, which provides a latch 125 for detachably capturing

the distal end 128 of the locking arm 114 when the locking arm 114 is deflected toward the base 120 and under the latch 125. (Basic flexible post-arm latching mechanisms are well known in the art and are in wide use with the conventional pincer clamps for central venous catheters used for dialysis.) The post 124 includes a bevel 126 facing distally so that inadvertent disconnection is minimized (as by contact pressure against the outer surface of the post 124). Such a distal orientation of the bevel 126 can direct contact force against the bevel toward the locking arm 114 rather than away from it. Alternatively the post 124 can be angled inwardly toward the locking arm 114 (for example 10-20 degrees from vertical) to direct such a force toward the locking arm 114.

Please paragraph [0041] with the following amended paragraph:

[0041] A presently preferred embodiment of the sequential catheter-flushing fluid lock system according to the present invention, which can substantially reduce the need to routinely access fluid lock systems, is shown in FIG. 7. Three low profile, catheter-flushing clamps 401, 402, and 404 are mounted in series upon tubing 404. Tubing 404 has enlarged portion 405 and closed proximal terminal 406 (shown as a luer receiving
valve) and a distal luer terminal 108, for connection with a catheter 409 at catheter hub 410. The catheter 409 has an internal lumen 411 defining a length shown as 414. These catheter-flushing clamps 401,402 and 404 are marked at both the top (thumb contact) surface 415 and the bottom surface with "1st, 2nd, and 3rd" to remind the nurse of the order of closure every 8 hours as will be discussed. The tubing 404 preferably has a generous internal diameter (for example in the

range of 4-6 mm) so that the flush volume generated by each catheter-flushing clamp is relatively high in comparison to the volume of the lumen 411 along length 414. In one example, a catheter-flushing clamp of the type for example shown in FIGS. 2-4 with a compression length of 9 mm mounted on tubing with a internal diameter of about 3.5-4 mm, can generate a flush volume exceeding the entire internal volume of the potential indwelling length 414 of a typical 1.5 inch 18 gauge catheter (as for example the "Insyte" catheter marketed by Becton Dickinson), so that the sequential closure of each of the three such flushing clamps 401,402,403, can achieve complete flushing of the lumen 411 of catheter 409 on three separate occasions without requiring the opening or internal access of the system 400. Yet the volume of the flush is low, predetermined, and discrete so as to minimize the amount of flush solution displaced into the patient's systemic system.

Please replace the **Abstract** with the following amended Abstract:

A catheter-flushing ~~fluid lock system (100)~~ extension tube for maintaining the patency and sterility of the lumen of an indwelling catheter ~~(203)~~. The system is comprised of an extension tube ~~a fluid locked system such as a tubing system (104)~~ in fluid connection with an indwelling catheter; the extension tube defines ~~said tubing system defining~~ an internal volume and at least one sealed proximal terminal ~~(106)~~ for intermittent connection with an external fluid source. The extension tube is configured such that the internal volume of the tube can be progressively reduced at a plurality of different times so that the extension tube itself provides the source of catheter flush solution for intermittently flushing the catheter.